

---

## Highly Efficient Differentiation of Functional Hepatocytes From Human Induced Pluripotent Stem Cells.

**Journal:** Stem Cells Transl Med

**Publication Year:** 2013

**Authors:** Xiaocui Ma, Yuyou Duan, Benjamin Tschudy-Seney, Garrett Roll, Iman Saramipour Behbahan, Tijess P Ahuja, Vladimir Tolstikov, Charles Wang, Jeannine McGee, Shiva Khoobyari, Jan A Nolte, Holger Willenbring, Mark A Zern

**PubMed link:** 23681950

**Funding Grants:** An in vitro and in vivo comparison among three different human hepatic stem cell populations.

### Public Summary:

Human induced pluripotent stem cells (hiPSCs) hold great potential for use in regenerative medicine, novel drug development, and disease progression/developmental studies. Here, we report highly efficient differentiation of hiPSCs toward a relatively homogeneous population of functional hepatocytes. hiPSC-derived hepatocytes (hiHs) not only showed a high expression of hepatocyte-specific proteins and liver-specific functions, but they also developed a functional biotransformation system including phase I and II metabolizing enzymes and phase III transporters. Nuclear receptors, which are critical for regulating the expression of metabolizing enzymes, were also expressed in hiHs. hiHs also responded to different compounds/inducers of cytochrome P450 as mature hepatocytes do. To follow up on this observation, we analyzed the drug metabolizing capacity of hiHs in real time using a novel ultraperformance liquid chromatography-tandem mass spectrometry. We found that, like freshly isolated primary human hepatocytes, the seven major metabolic pathways of the drug bufuralol were found in hiHs. In addition, transplanted hiHs engrafted, integrated, and proliferated in livers of an immune-deficient mouse model, and secreted human albumin, indicating that hiHs also function in vivo. In conclusion, we have generated a method for the efficient generation of hepatocytes from induced pluripotent stem cells in vitro and in vivo, and it appears that the cells function similarly to primary human hepatocytes, including developing a complete metabolic function. These results represent a significant step toward using patient/disease-specific hepatocytes for cell-based therapeutics as well as for pharmacology and toxicology studies.

### Scientific Abstract:

Human induced pluripotent stem cells (hiPSCs) hold great potential for use in regenerative medicine, novel drug development, and disease progression/developmental studies. Here, we report highly efficient differentiation of hiPSCs toward a relatively homogeneous population of functional hepatocytes. hiPSC-derived hepatocytes (hiHs) not only showed a high expression of hepatocyte-specific proteins and liver-specific functions, but they also developed a functional biotransformation system including phase I and II metabolizing enzymes and phase III transporters. Nuclear receptors, which are critical for regulating the expression of metabolizing enzymes, were also expressed in hiHs. hiHs also responded to different compounds/inducers of cytochrome P450 as mature hepatocytes do. To follow up on this observation, we analyzed the drug metabolizing capacity of hiHs in real time using a novel ultraperformance liquid chromatography-tandem mass spectrometry. We found that, like freshly isolated primary human hepatocytes, the seven major metabolic pathways of the drug bufuralol were found in hiHs. In addition, transplanted hiHs engrafted, integrated, and proliferated in livers of an immune-deficient mouse model, and secreted human albumin, indicating that hiHs also function in vivo. In conclusion, we have generated a method for the efficient generation of hepatocytes from induced pluripotent stem cells in vitro and in vivo, and it appears that the cells function similarly to primary human hepatocytes, including developing a complete metabolic function. These results represent a significant step toward using patient/disease-specific hepatocytes for cell-based therapeutics as well as for pharmacology and toxicology studies.